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EXAMINER	
MCGARRY, SEAN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,811	MACCALMAN, COLIN D.	
	Examiner	Art Unit	
	Sean R McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7, 9-15, and 19-24* is/are pending in the application.

4a) Of the above claim(s) *2, 5-7, 13-15, 19, and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 9-12, and 21-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3, 4, 9-12, and 21-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claimed invention is drawn to the modulation of differentiation or neoplastic transformation of cells via the administration of antisense or sense oligonucleotides to cad-11. the invention is drawn to the treatment cancer and for the process of preventing or terminating a pregnancy via antisense oligonucleotides targeted to cad-11.

The specification discloses SEQ ID NO: 1 and 2 that are antisense oligonucleotides that bind to and inhibit Cad-11 in cells in culture. The specification now discloses SEQ ID NO: 5 which is a specific sequence encoding a cad-11 and is the sequence used to make SEQ ID NOS: 1 and 2. However, the claims claims are so broad as to encompass the use of any antisense or sense oligonucleotide targeted to any form of what may be considered cad-11 (for example, sequences that are substantially identical or which will hybridize to or contain nucleotide sequences of SEQ ID NO: 1 or 2 or 5, antisense or sense targeted to corresponding sequences from other species, mutated sequences, allelic variants, splice variants, etc.). The specification discloses two antisense oligonucleotides that inhibit cad-11 in culture and no sense oligonucleotides that have any activity required for their use in the claimed invention.

The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the use SEQ ID NO: 1 and 2 in cells in culture, the skilled artisan cannot envision the detailed chemical structure of the encompassed antisense or sense oligonucleotides required for use in the methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993). University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant

complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA

itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

The instant specification provides only two examples of antisense oligonucleotides used in a cell culture and provides no examples of sense oligonucleotides with any activity that would be required for use in the claimed methods. The specification does not provide sufficient examples such that one would know the structure of compounds required for the practice of the claimed method, for example. The specification does not provide what the structure/sequence of the antisense or sense oligonucleotides required for use in the methods would be. The determination of effective antisense oligonucleotides is **empirical**. Branch [TIBS Vol. 23, February 1998] addresses the need to empirically find antisense sequences with the following statements: "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined **empirically** by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is

beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

Applicant appears to be claiming a method of treatment where a compound that is necessary to practice that method is described only in terms of its function (ie to inhibit expression such that a treatment in vivo is effected). The specification provides only two antisense oligonucleotides that inhibit in cell culture where the only means left for one to find compounds that function in claims is by a trial and error process.

Applicant's arguments filed 5/20/04 have been fully considered but they are not persuasive.

Applicant essentially argues that the specification provides adequate description since two species of antisense oligonucleotides have been disclosed and since the specification provides methods by which potential antisense or sense oligonucleotides could be selected. It is asserted that one in the art could recognize potential sense and antisense oligonucleotides and further test whether they actually possess the required activity for use in the claims. It appears that one in the art would recognize the potential oligonucleotides based solely on whether they contain or are complementary to a cad-11 sequence. Applicant asserts that the citation of University of California v. Eli Lilly and Co., 43 USPQ2d 1398 (CAFC 1997) is improper since the facts of that case are different than that of the instant application. It is noted that applicant does not address

that which was relied uponin of University of California v. Eli Lilly and Co., 43 USPQ2d 1398 (CAFC 1997) in the rejection of record, for example:

> Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Applicant ignores the rejections reliance on Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993). "Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. ", for example.

Applicant also argues that it is improper to rely on the unpredictability in the art to support a rejection for lack of adequate written description in response to the examiners citation of Branch et al. The citation of Branch et al in the above rejection evidences the fact that there is no art recognized structure that imparts any specific activity for an antisense molecule, for example. It evidences that the structure (sequence) of any and every antisense oligonucleotide must be determined empirically. The determination of the structure for the function of any particular antisense is done de novo for each and every antisense molecule. The instant specification does not provide any particular structure that would impart the function of inhibiting cad-11 such that one would know the sequence/structure of antisense molecules that have the function of inhibiting a cad-11 as required in the claimed methods. The mere containing of sequence of a cad-11 encoding nucleic acid or complementary to a nucleic acid encoding cad-11 does not impart the capacity to inhibit cad-11 as required for use in the instantly claimed methods. One in the art is left with using a trial and error method of finding potential antisense or sense oligonucleotides for use in the claimed methods.

Claims 1, 3, 4, 9-12, and 21-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant invention is drawn to methods of treating cancer and for the prevention or aborting of pregnancy via the administration of antisense or sense oligonucleotides. The instant specification shows that the administration of antisense (OB-1) to prostate cancer cells caused loss of cell viability in these cells and showed that administration of the same antisense to trophoblast cells caused cells to fail to upregulate cad-11 and became, over time, unviable. The specification provides general guidance for the methods of the inventions but does not provide any specificity in the practice of the claimed methods.

The specification fails to provide guidance or examples that would show by correlation the practice of the instant invention such that a treatment or prevention of pregnancy or abortion of a pregnancy is effected. The art of antisense therapy is an unpredictable art where specific guidance in the antisense sequence and modes of delivery of antisense oligonucleotides for any particular treatment (a specific cancer, for example) is needed.

Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug

design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is

the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*." Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome. Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby

interfering in the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . .[i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations." (Page 379).

The references above clearly show that the art of antisense therapy is an unpredictable art and evidence that the general guidance provided in the instant specification is not sufficient for one in the art to practice the instant invention without the need to perform undue trial and error experimentation. The undue trial and error experimentation including, finding effective antisense sequences that may be useful in any particular disease or cell type, and also to find an effective mode of delivery for the treatment of any condition in an in vivo environment where the art has shown this delivery to be unpredictable, for example.

Applicant's arguments filed 5/20/04 have been fully considered but they are not persuasive.

Applicant has argued that the examiner has essentially stated that any claim pertaining to antisense therapy is automatically in a suspect field and that, absent proof of a completely reliable cures in a human patients, their can be no patents in the field of antisense therapy. This is not the case. The examiner explained "The specification fails to provide guidance or examples that would show by correlation the practice of the instant invention such that a treatment or prevention of pregnancy or abortion of a pregnancy is effected. The art of antisense therapy is an unpredictable art where specific guidance in the antisense sequence and modes of delivery of antisense oligonucleotides for any particular treatment (a specific cancer, for example) is needed."

The art cited by the examiner then evidenced the obstacles to the routine use of antisense in therapies such as sequence determination of a therapeutic oligonucleotide and methods of effective delivery. It was explained that the general guidance of the specification does not ensure one of skill in the art sufficient guidance to perform the claimed invention without the need to perform undue trial and error experimentation. Applicant has not explained how the instant specification as filed provide adequate guidance in view of the relevant art cited by the examiner or that the cited art is not applicable to the claimed invention. The specification provided only general guidance and does not provide sufficient guidance how one would provide sufficient amounts of any particular antisense in the appropriate cells to prevent a pregnancy or how to

administer sufficient amounts of antisense to cells required to terminate a pregnancy, for example. The art cited y the examiner indicates that one cannot necessarily correlate in vitro or cellular observations to in vivo efficacy. Applicant's response does not provide arguments or evidence that the instant specification shows such a correlation has been established or that the art cited does not apply to the instant invention. Applicant essentially points to general teachings in the specification and asserts that the rejection is wrong. Applicant has not shown that the art of antisense therapy is predictable based on the prior art or the specification as filed, for example.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sean R McGarry
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srm